CryoSYNC gel: A Novel Nanoparticle and Biocompatible Gel to Enhance Performance of Cryoablation

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INTRODUCTION

Cryoablation is a procedure in which an extremely cold liquid or an instrument called a cryoprobe is used to freeze and destroy abnormal tissue. A cryoprobe is cooled with substances such as liquid nitrogen, liquid nitrous oxide, or compressed argon gas based on Joule-Thompson effect as a working principle.[1] Alternating cycles are used to make destruction of tumor cells more effective. The cryoablation procedure can be used freeze-thaw to treat a variety of conditions, including breast cancer, prostate cancer, liver cancer, and kidney cancer.[2,3]

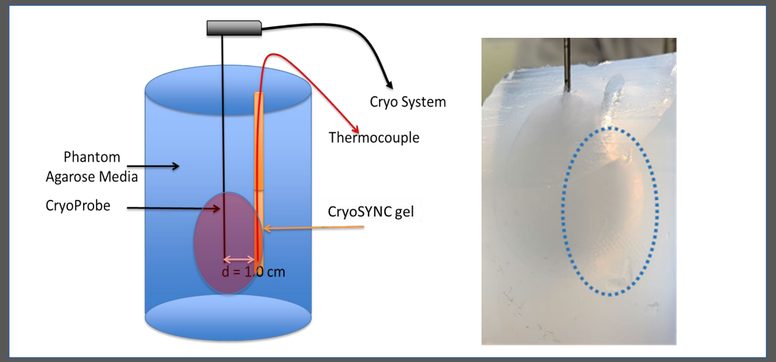
Cryoablation occurs in tissue that has been frozen by at least three mechanisms[4]: 1. Formation of ice crystals within cells thereby disrupting membranes, and interrupting cellular metabolism among other processes; 2. Coagulation of blood thereby interrupting blood flow to the tissue in turn causing ischemia and cell death; and 3. Induction of apoptosis, the so-called programmed cell death cascade.

However, cryoablation suffers from its shortcomings: 1. it is difficult to ablate tumor size larger than 3 cm in diameter; 2. Cryoablation procedure takes relatively longer time (> 30 minutes) to ensure the entire target area reaches the temperature < -40 °C; 3. Imaging (e.g., CT) cannot distinguish the target temperature i.e., < -40 °C from ice ball (< 0 °C). For these reasons, tumor recurrence rates can be as high as 80%.[5]

Here, Theromics has developed a gel-like material that can be injected to a periphery of tumor at 1-1.5 cm from a cryoprobe and achieve < -40 °C within 5 minutes than the case without gel. This material, CryoSYNC gel, is also designed in such a way that immunomodulatory drugs can be mixed with the gel. Such ability allows the drug (e.g., TLR or STING agonists, immune checkpoint inhibitors) to be released to recruit anti-tumor immune responses as suggested in the literature.[6]

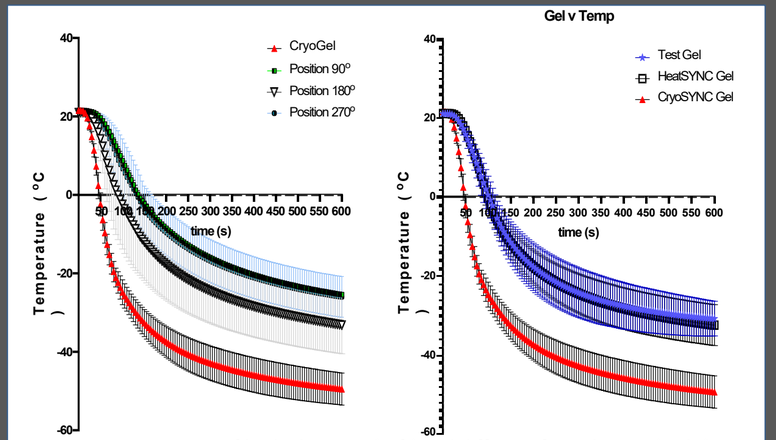
MATERIALS AND METHODS

To a 150 mL agarose (1 %(w/v) agarose, Bio-RAD) phantom, 5 cm from the surface, a cylindrical (0.5 cm diameter) hole was bored, to which CryoSYNC gel (0.5 mL) was added without any bubbles. Four thermocouples (Type K) were placed at 90° to each other, 1-1.5 cm from a cryoprobe (PCS17): 270 ° (gel); 0 °, 90 °, 180 ° (phantom). The thermocouples were connected to a temperature data logger (Digilent MCC WebDAQ 316, 16 thermocouple ports) to process multiple subzero temperature data. The cryoprobe is connected to EndoCare Cryoablation system (Varian) with an argon tank. Cryoablation was performed for 10 minutes for all experiments. The same procedure was performed in a bovine liver tissue.

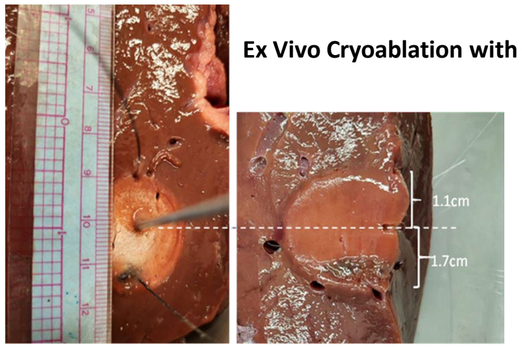


RESULTS AND DISCUSSION

Several gel samples with different formulations consisting commonly of a human protein as a major component were tested. All formulations showed lower than the temperatures at same distance and different positions. One formulation in particular, CryoSYNC gel showed < -40 °C before 5 minutes (-50 °C at 10 minutes) while two other formulations showed -24.5 °C at 5 minutes and ca. -30 °C at the end of the experiments. The ex vivo experiment demonstrated the consistent profile as obtained in the in vitro studies. One hour post ablation, the affected area of the liver tissue showed lighter in color than other area and appeared swollen. The gel injected site was distinguishable from the rest of the ablated area. The lateral dissection revealed that the length to the periphery (the gel side) was longer (1.7 cm) than the other side (1.1 cm). Several gel samples with different formulations consisting commonly of a human protein as a major component were tested. All formulations showed lower than the temperatures at same distance and different positions. One formulation in particular, CryoSYNC gel showed < -40 °C before 5 minutes (-50 °C at 10 minutes) while two other formulations showed -24.5 °C at 5 minutes and ca. -30 °C at the end of the experiments. The ex vivo experiment demonstrated the consistent profile as obtained in the in vitro studies. One hour post ablation, the affected area of the liver tissue showed lighter in color than other area and appeared swollen. The gel injected site was distinguishable from the rest of the ablated area. The lateral dissection revealed that the length to the periphery (the gel side) was longer (1.7 cm) than the other side (1.1 cm).



Temperature profiles by location (Left) and different formulations (Right)



Ex Vivo Cryoablation with CryoSYNC gel

CONCLUSIONS

Temperature depression by CryoSYNC gel is far superior to other formulas during cryoablation to achieve the tumoricidal temperature (< -40 °C). Physicochemical and thermodynamic characterizations of the gel are currently performed. Further applications of the gel is also pursued: For example, immunomodulatory drug delivery.

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